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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) ONYX1046.ORD

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on 25 August 2005

Signature Gary R Fabian

Typed or printed name Gary R. Fabian

Application Number	Filed
09/410,462	1 Oct 1999

First Named Inventor: A. Williams

Art Unit	Examiner
1635	J.E. Angell

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record. Registration number 33,875

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Gary R Fabian
Signature

Gary R. Fabian, Ph.D.
Typed or printed name

650-780-9030
Telephone number

25 August 2005
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of One forms are submitted.

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Gary A Fabian — 25 Aug 2005
Signature — Date of Transmittal

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE	
In Re Application of: Williams, A., et al.	Confirmation No. 6889
Serial No.: 09/410,462	Art Unit: 1635
Filing Date: 1 October 1999	Examiner: J.E. Angell
Title: A SINGLE AGENT METHOD FOR KILLING TUMOR AND TUMOR ASSOCIATED ENDOTHELIAL CELLS USING ADENOVIRAL MUTANTS	

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Advisory Action in the above-referenced application, mailed 25 July 2005. Applicants respectfully request review of the following rejections before filing of the Appeal Brief.

I. Rejection of Claims 1-6 Under 35 U.S.C. §102(e).

The Examiner maintained the rejection of claims 1-6 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al. (U.S. Patent No. 6,080,578). The following comments provide further support for applicants remarks presented in the Response to Final Rejection, filed 20 June 2005, pages 16-18.

Clear errors in the Examiner's rejection:

In the Advisory Action the Examiner states the following rejection based on "inherency":

> Applicant is reminded that MPEP 2112.02 indicates, "When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPT 136 (Fed. Cir. 1986)." In the instant case, Bishoff teaches a method comprising administering a vector encompassed by the

claims to a tumor in an animal. It is noted that tumors comprise dividing cancer cells and dividing endothelial cells (e.g., vascular cells of the tumor). Therefore, the method taught by Bishoff must, by necessity, result in killing of the dividing cells of the tumor, which would include dividing cancer cells and dividing endothethial cells. (Advisory Action, last paragraph.)

To support an anticipation rejection based on inherency, an Examiner must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the prior art. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Pending claim 5 recites "said adenovirus mutation in E1A RB family member binding region of said virus is in the E1A-CR2 region." Pending claim 6 recites "said mutation in the E1A-CR2 region comprises a deletion or substitution of one or more amino acids 111 through 123." The specification recites, for example, the following regarding mutations specifically in the E1A-CR2 region:

> In another aspect of the invention, replication competent adenoviral mutants that exhibit a mutation in the RB family member binding region of E1A, **preferably the E1A-CR2 region**, are capable of enhanced replication compared to wild type adenovirus in dividing normal or cancer cells. (Specification, page 3, lines 23-26, emphasis added.)
> **The enhanced replication and cytopathogenicity of E1A-CR2 RB binding site mutants versus wild-type adenovirus in proliferating cells was unexpected.** Indeed, several adenovirus and herpes virus mutants are known that have been genetically attenuated in order to achieve selective replication in tumor cells. See, Heise, C. *et al., Nat. Med.* 3, 639-645 (1997); Bischoff, J.R. *et al., Science* 274, 373-376 (1996); Martuza, R.L., *et al., Science* 252, 854-856 (1991); Mineta, T., *Nat Med* 1, 938-943 (1995). Each of these attenuated viruses replicates less efficiently than its wild-type parental virus, even in tumor cells. See, Bischoff, J.R. *et al., Science* 274, 373-376 (1996); Martuza, R.L. *et al., Science* 252, 854-856 (1991); Kirn, D.H., *Expert Opinion on Investigational Drugs* 5, 753-762 (1996). In some cases replication can be reduced by 10 to 100-fold versus the wild-type virus. See, Martuza, R.L. et al., *Science* 252, 854-856 (1991). This is presumably due to the loss of important viral functions that enhance replication. The reason for the enhanced replication of E1A-CR2 RB binding mutants versus wild-type adenovirus is unknown. It will be apparent to the skilled practitioner of this art that the E1A RB binding site mutants disclosed herein, and **preferably the E1A-CR2 RB binding site mutants, have a large therapeutic index between dividing and quiescent cells, or more specifically, tumor and proliferating microvascular endothelial cells, and quiescent microvascular endothelial cells.** (Specification, page 13, line 29, to page 14, line 15, emphasis added.)

These features of the present invention do not "necessarily flow" from the teachings of the reference of Bischoff, et al. The reference of Bischoff, et al., contains no teaching or suggestion directing one of ordinary skill in the art to specifically use mutations in the E1A-CR2

region of the E1A RB family member binding region for substantial and selective killing of dividing cells comprising cancer and endothelial cells (see, pending claim 1 and dependent claims 5 and 6 of the present application); in particular, the reference of Bischoff, et al., contains no teaching or suggestion regarding the unexpected and superior properties of mutations in the E1A-CR2 region comprising a deletion or substitution of one or more amino acids 111 through 123 (i.e., claim 6 of the present application).

For a claim to be inherent in the prior art it "is not sufficient that a person following the disclosure sometimes obtain the result set forth in the [claim]; it must invariably happen" (*Standard Oil Co. v. Montedison, S.p.A.*, 664 F.2d 356, 372, 212 USPQ 327, 341 (3d Cir. 1981). Following the teaching of the reference of Bischoff, et al., that mutations in either the CR1 and/or CR2 domains of E1A result in replication deficient adenovirus constructs (see, Bischoff, et al., col. 9, line 20, to col. 11, line 20), it **does not invariably** give rise to the method of applicants' claims 5 and 6. Accordingly, the reference of Bischoff, et al., cannot be said to inherently anticipate the invention of at least claims 5 and 6 of the present application.

Further, the reference of Bischoff, et al., neither teaches nor suggests the unexpected and superior properties E1A-CR2 RB binding site mutants for use in the methods of the present invention. The reference of Bischoff, et al., does not teach or suggest that the E1A-CR2 RB binding site mutants have unexpected and superior properties to mutations elsewhere in the E1A RB binding site. Accordingly, applicants submit that there is clear error in the Examiner's rejection of at least claims 5 and 6 under 35 U.S.C. §102(e) for the reasons presented above.

II. Addressing the Examiner's Rejection of Claims 1-20 under 35 U.S.C. §112, First Paragraph.

The Examiner maintained the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, asserting that the specification, "while being enabling for methods of reducing the size of a tumor by the intratumoral injection of Ad5 vector disclosed as dl922/947, dl1107 or pm 928, does not reasonably provide enablement for the full scope of the claims." (Office action, dated 20 April 2005, page 2). The following comments support applicants' remarks presented in the Response to Final Rejection, filed 20 June 2005, pages 5-16.

The Examiner's Omission of Essential Elements Needed for a *Prima Facie* Rejection:

First, in the context of *in vivo* administration the Examiner asserted literature support for

the rejection by citing the teachings of the references of Dang, et al, (Clinical Cancer Research 5:471-474, Feb. 1999) and Eck, et al., (Goodman & Gillman's *The Pharmaceutical Basis of Therapeutics*, Chapter 5 Gene Based Therapy, pages 77-101). The Examiner generically applied these references to the areas of gene therapy and gene transfer *in vivo*. Subsequently, applicants rebutted the Examiner's references and arguments (see, for example, Response to Final Rejection, dated 20 June 2005, pages 6-7, and pages 10-15) with reference to the specification of the presently pending application, as well as by providing specific references in the field of oncolytic adenoviruses to support their position, for example U.S. Patent Nos. 5,998,205, 5,698,443, 5,677,178, and 6,080,578, as well as the following two references: Journal of Virology, July 2000, page 6147, Journal of Virology, March 2001, page 2857.

The Examiner has provided no further evidence or arguments to rebut the teachings of the references referred to by the applicants nor has the Examiner provided any reasoning as to why the generic teachings of Deng, et al, and Eck, et al., support the Examiner's asserted rejection even in view of the teachings of the references provided by the applicants specifically regarding oncolytic adenoviruses. Whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See, e.g., In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). Accordingly, the Examiner has failed to establish a *prima facie* rejection under 35 U.S.C. §112, first paragraph, for at least the reasons set forth above.

Second, regarding the limitation of the claims by the Examiner to "the Ad5 vector disclosed as dl922/947, dl1107 or pm 928," the asserted rejection has (i) not been supported by acceptable evidence, and (ii) not been supported by reasoning to contradict the applicants' claim. In particular, the Examiner has presented no reasoning, supported by the current literature as a whole, to buttress the rejection; whereas applicants have described the identification and characterization of adenoviral mutants of the present invention (see, for example, Response to Final Rejection, dated 20 June 2005, page 9). Accordingly, the Examiner failed to establish a *prima facie* rejection under 35 U.S.C. §112, first paragraph, at least for the above reasons.

Applicants submit that essential elements needed for a *prima facie* rejection under 35 U.S.C. §112, first paragraph, have been omitted by the Examiner for the reasons presented

above.

Clear Errors in the Examiner's Rejection:

The Examiner is relying on improper standards for enablement of the claimed invention (see, for example, Response to Final Rejection, dated 20 June 2005, pages 11-14). Accordingly, applicants submit that there is clear error in the Examiner's rejection of claims 1-20 under 35 U.S.C. §112, first paragraph.

III. Regarding the Examiner's Rejection of Claims 22-24 and 26-28 under 35 U.S.C. §112, Second Paragraph.

If, following findings 2 or 3 of the pre-appeal guidelines (Official Gazette, July 12, 2005, Vol. 1296, No.2), (i.e., prosecution of the present application is re-opened, or the application is allowed), then applicants respectfully request inclusion of amended claims 22-24 and 26-28. The Examiner denied entry of the amendment to these claims prior to appeal. However, applicants submit that there is no unduly burdensome additional search or consideration required for these claims, particularly in view of the fact that the adenoviral mutants embraced by these claims are also the subject of pending claims 8, 9, 10, 19, and 20. Further, the Examiner has suggested that the claims are enabled for the adenoviral mutants dl922/947, dl1107, and pm928 which are the subject matter of amended claims 22-24 and 26-28 (see, e.g., Advisory Action, continuation sheet 1, second paragraph).

Conclusion

Please direct all further communications in this application to:
Gregory Giotta, Ph.D., Esq.
ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Facsimile: (510) 597-6610.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502.

Respectfully submitted,

Date: 25 Aug 2005 By: Gary R Fabian

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